CARs for Pediatric Cancers

Nathan Singh
The Children's Hospital of Philadelphia
Perelman School of Medicine at the
University of Pennsylvania

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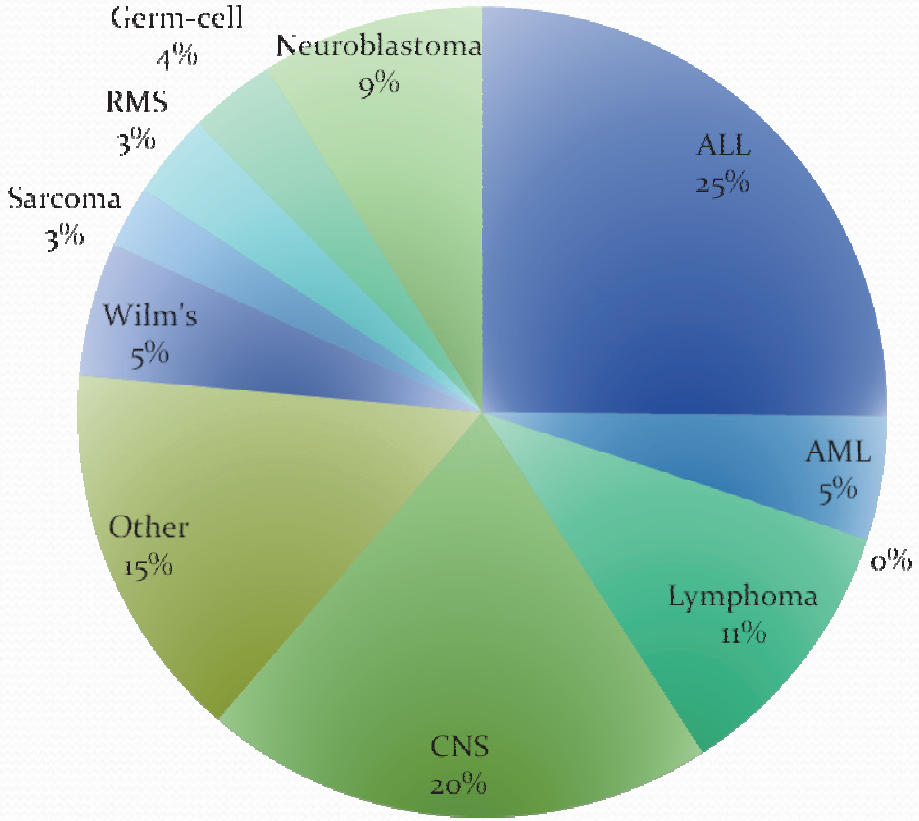
Presenter Disclosure Information

Nathan Singh

The following relationships exist related to this presentation:

No relationships to disclose

Childhood cancer



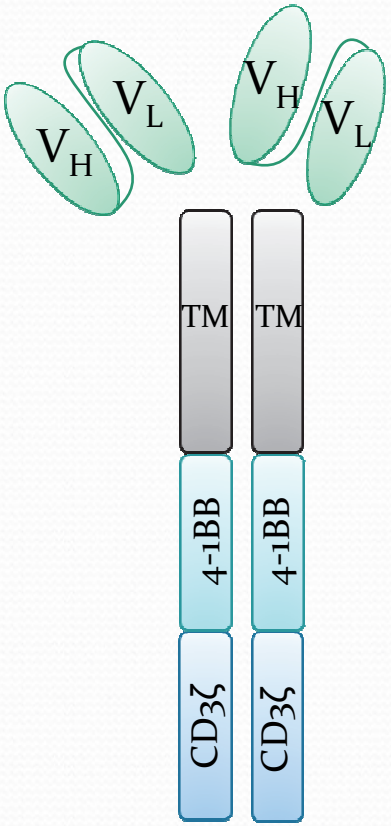
ALL

- 80-85% 5y EFS
- ~21% of pediatric oncology deaths

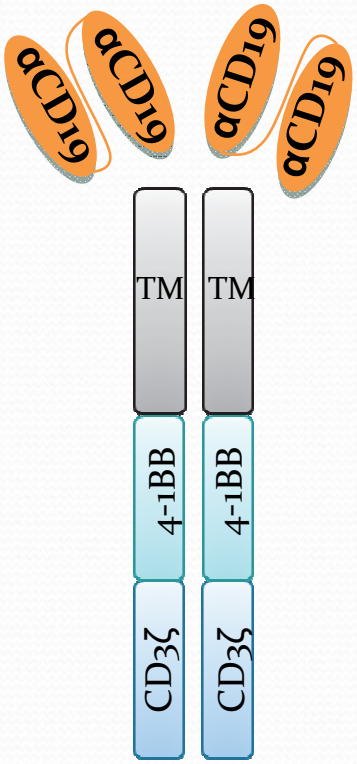
Neuroblastoma

- ~45% 5y EFS
- ~15% of pediatric oncology deaths

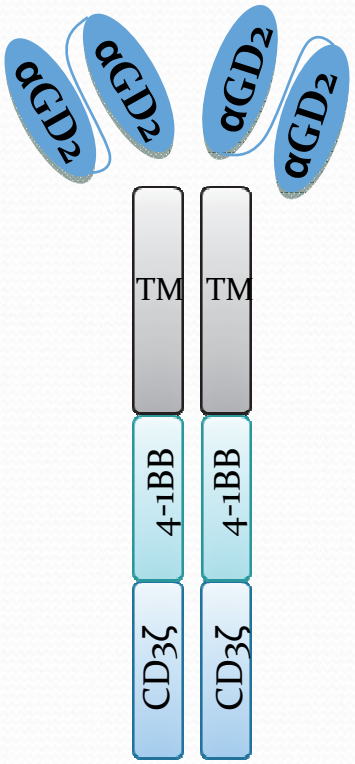
Chimeric Antigen Receptors



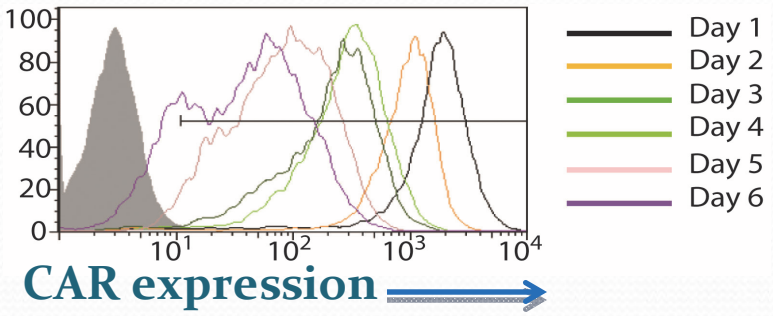
"CART19"



GD2 CAR



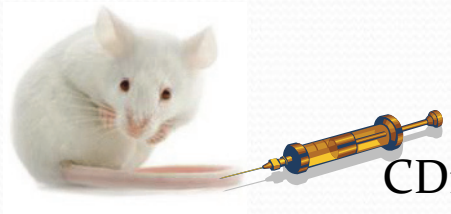
T-cell engineering



	Permanent	Transient
Method	Lentiviral transduction	RNA electroporation
Benefits	Sustained activity Potential memory response	Short-term toxicity Cheap(er)
Limitations	Persistent toxicity Expensive ? Insertional mutagenesis?	Limited activity

ALL

Xenograft model of ALL

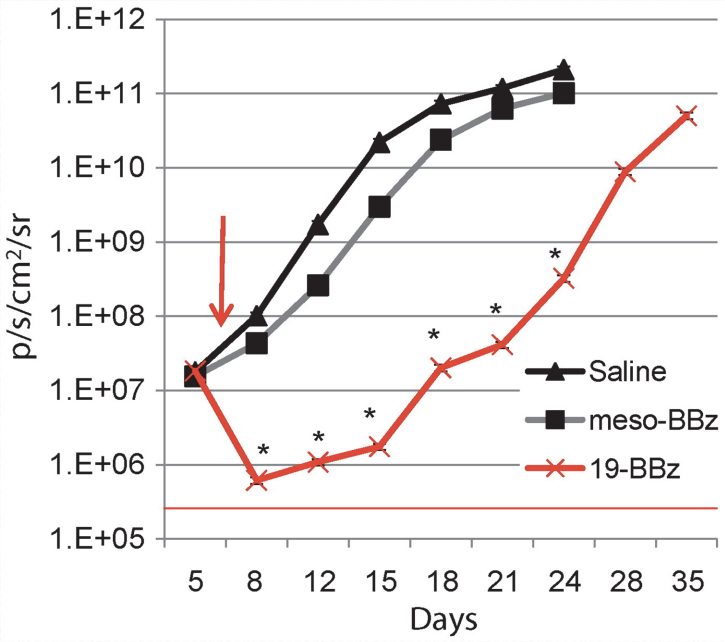


7d

CD19+ ALL

Lenti CART19 cells OR
RNA CART19 cells

NOD/SCID/$\gamma c^{-/-}$
(NSG)

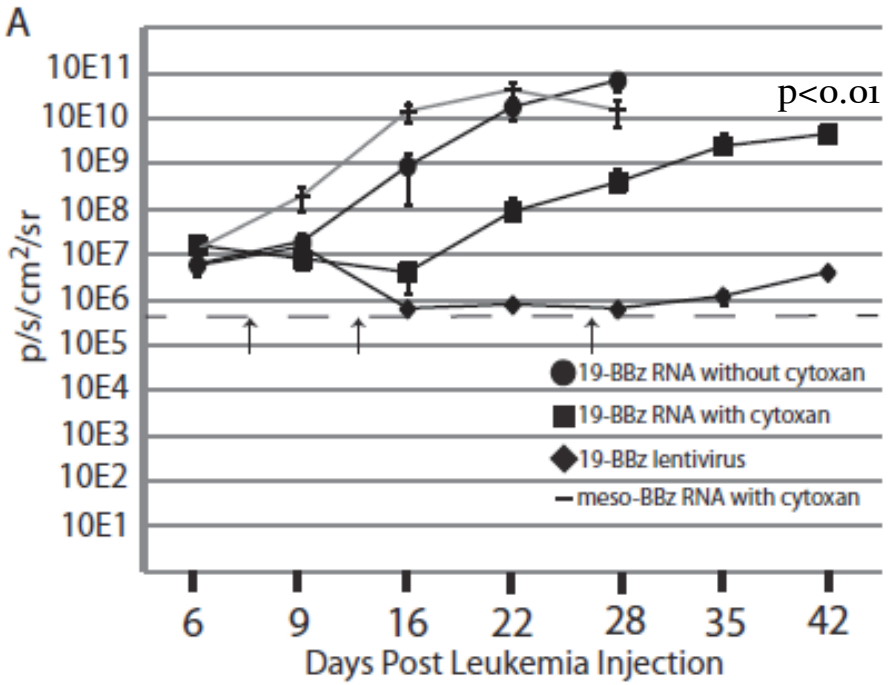


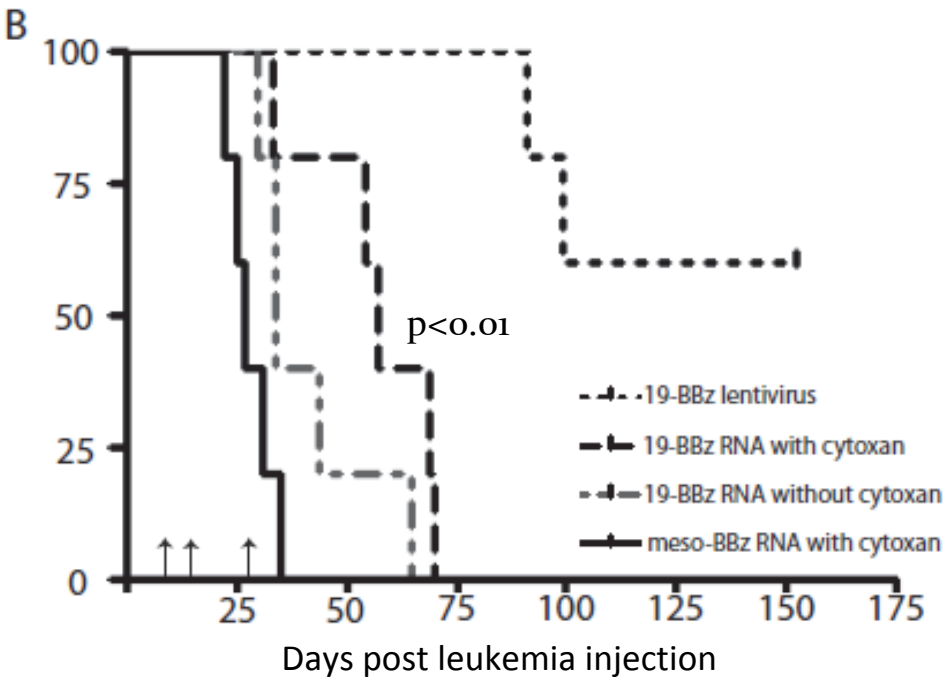
Multiple infusions?

Lymphodepletion?

Barrett DM et al.
Human Gene Therapy. 2011

RNA CARs: role of lymphodepletion

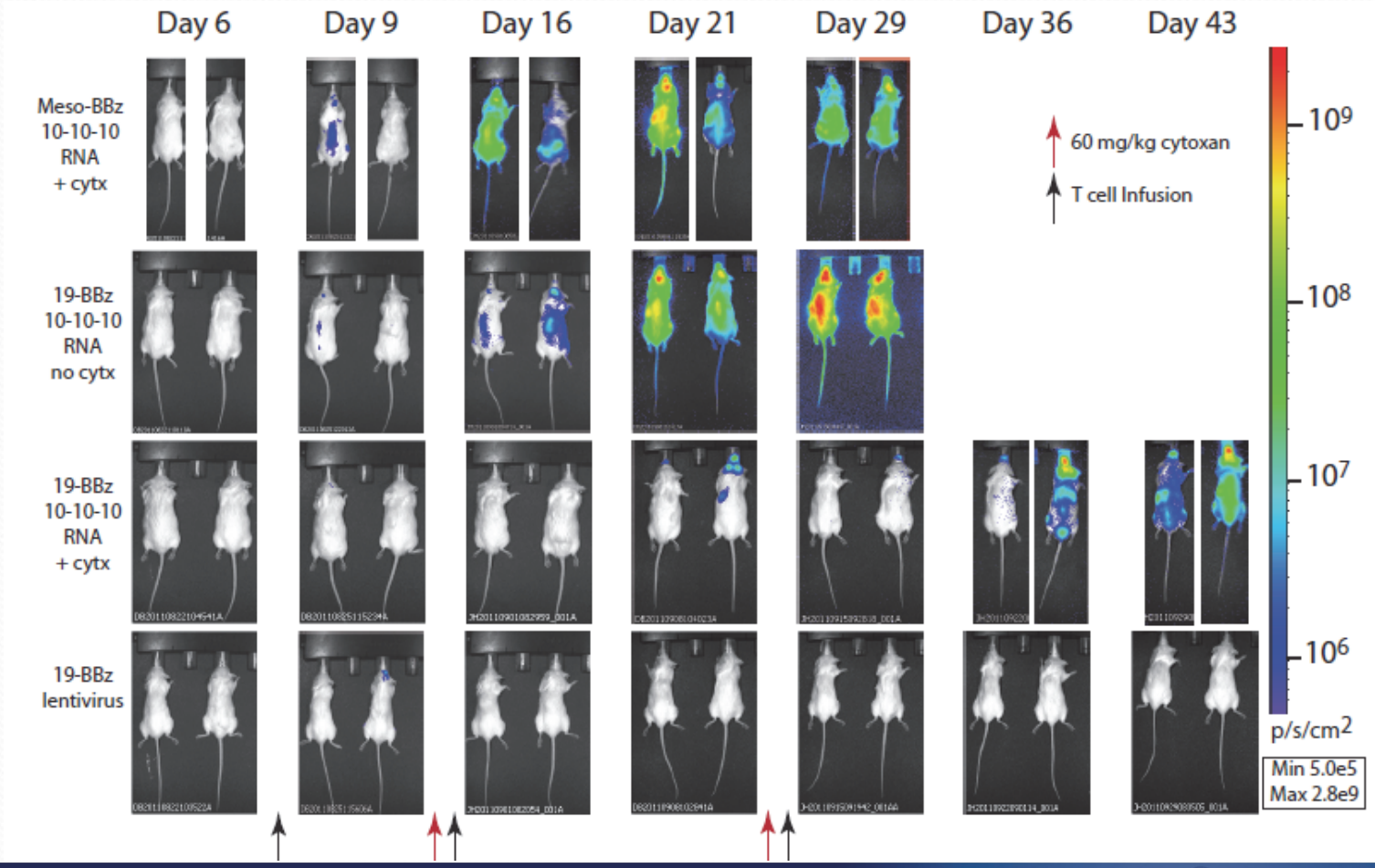




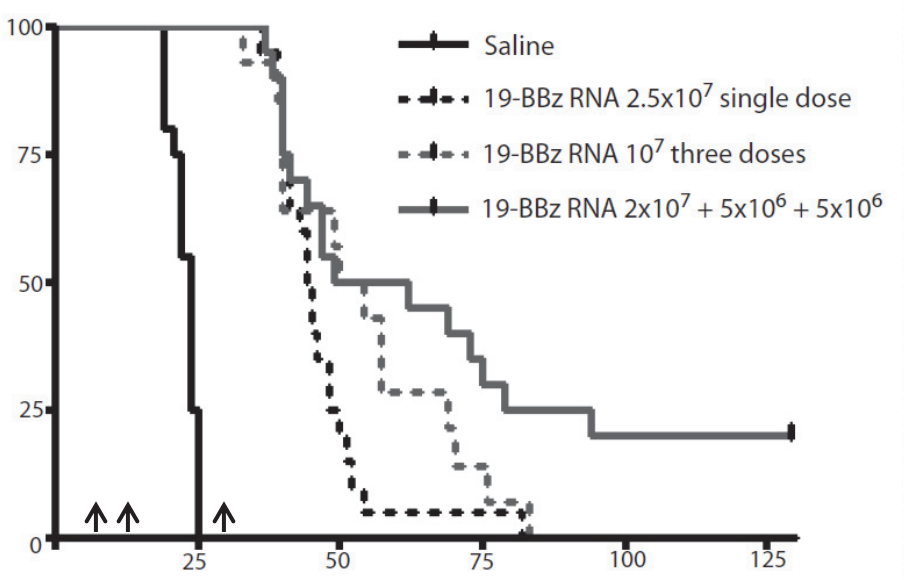
↑ 1 x 10⁷ RNA CART19 cells on days 7, 14, 28 or
1 x 10⁷ Lenti CART19 cells on day 7

19-BBz RNA no cytoxan median overall survival: 28d
19-BBz RNA + cytoxan median overall survival: 56d

RNA CARs: role of lymphodepletion

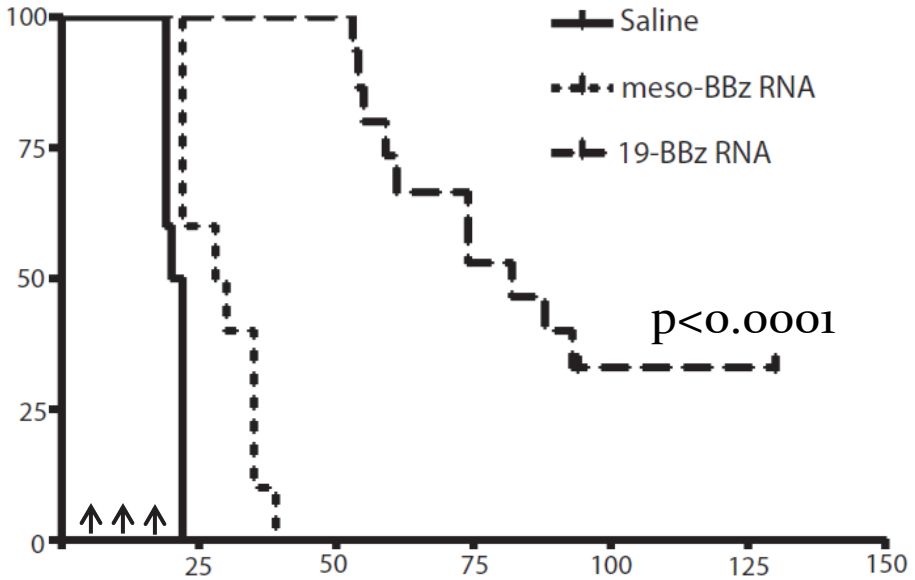


RNA CARs: dose splitting



Days post leukemia injection

↑ RNA CART19 cells
1 dose on day 7 or
3 doses on days 7, 14, 28



Days post leukemia injection

↑ RNA CART19 cells
2 x 10^7 on day 7
5 x 10^6 on days 14 and 21

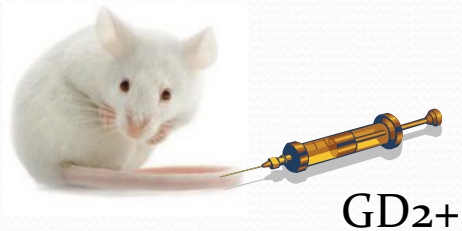
Neuroblastoma

Xenograft model of neuroblastoma

GD2+ NB
S.Q.

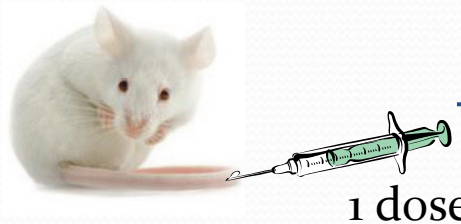
2W

3 doses GD2 RNA CAR T-cells



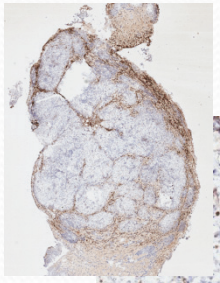
1-2W

GD2+ NB
I.V.

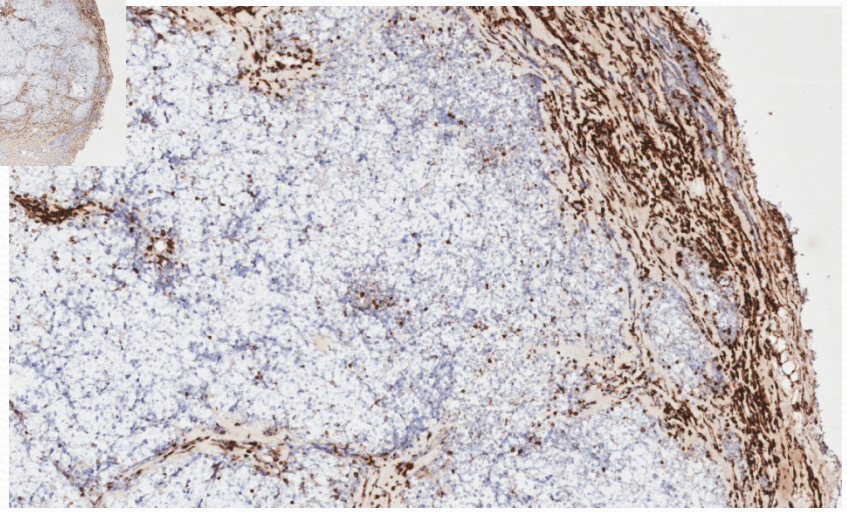


1 dose GD2 Lenti CAR T-cells
OR
3 doses GD2 RNA CAR T-cells

GD2 RNA CARs for flank NB

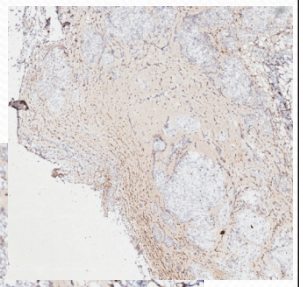


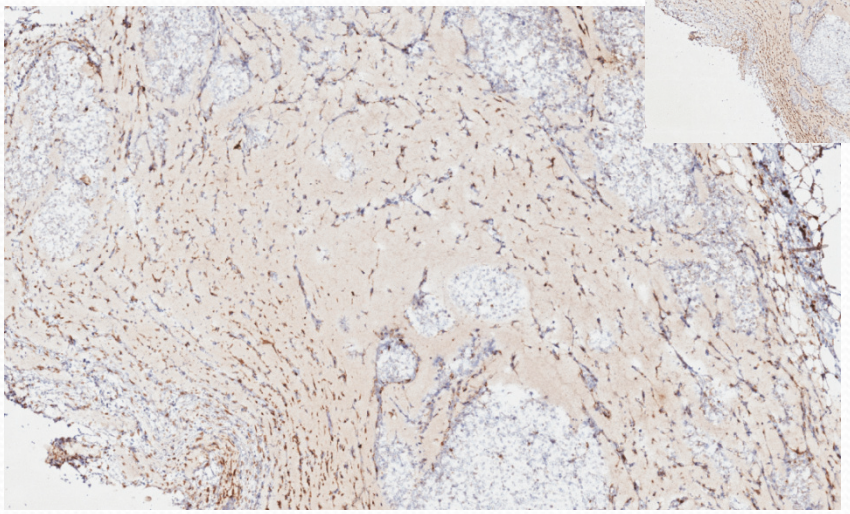
1X RNA CART19



4X

GD2 RNA CAR 1X

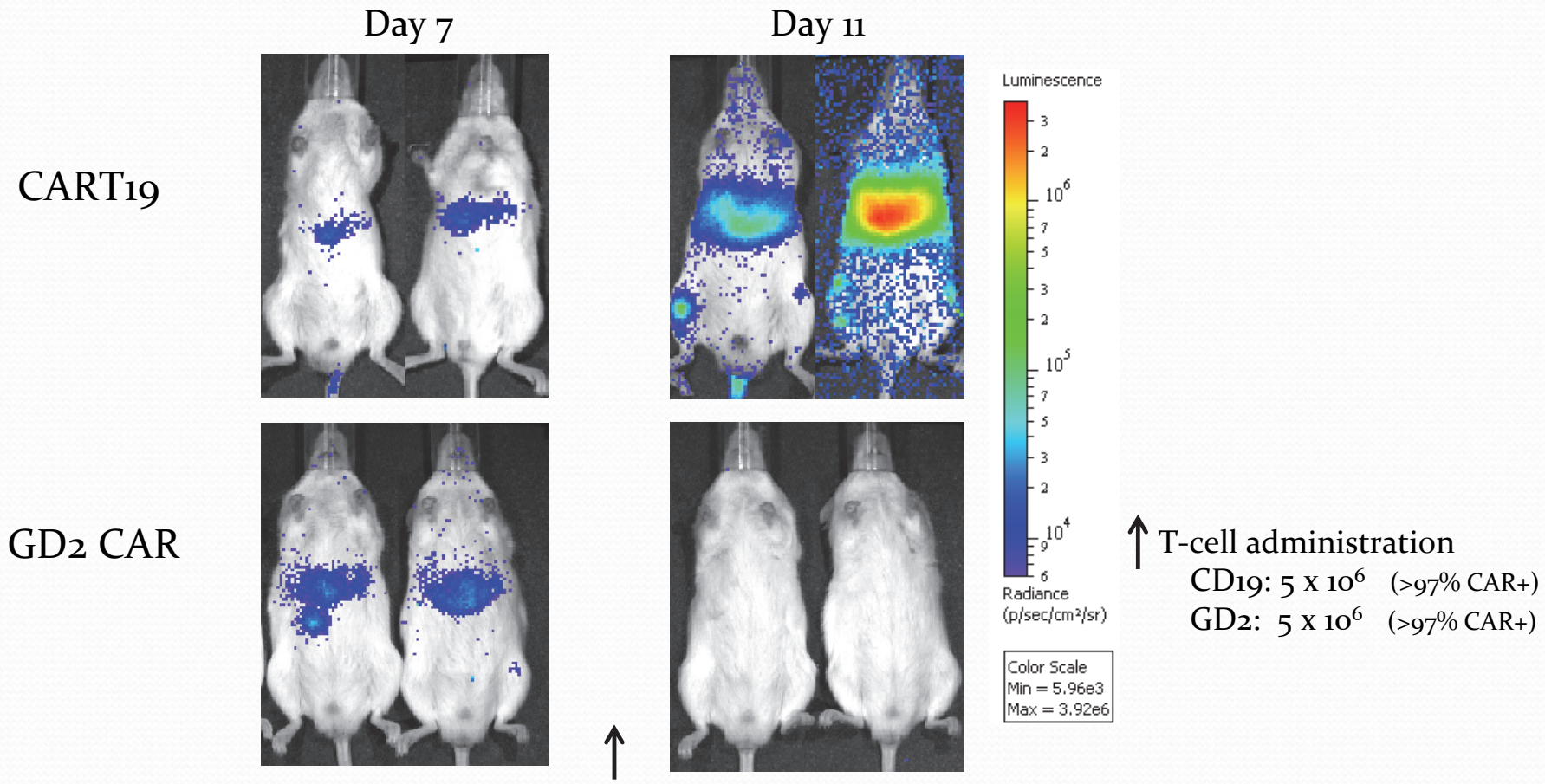




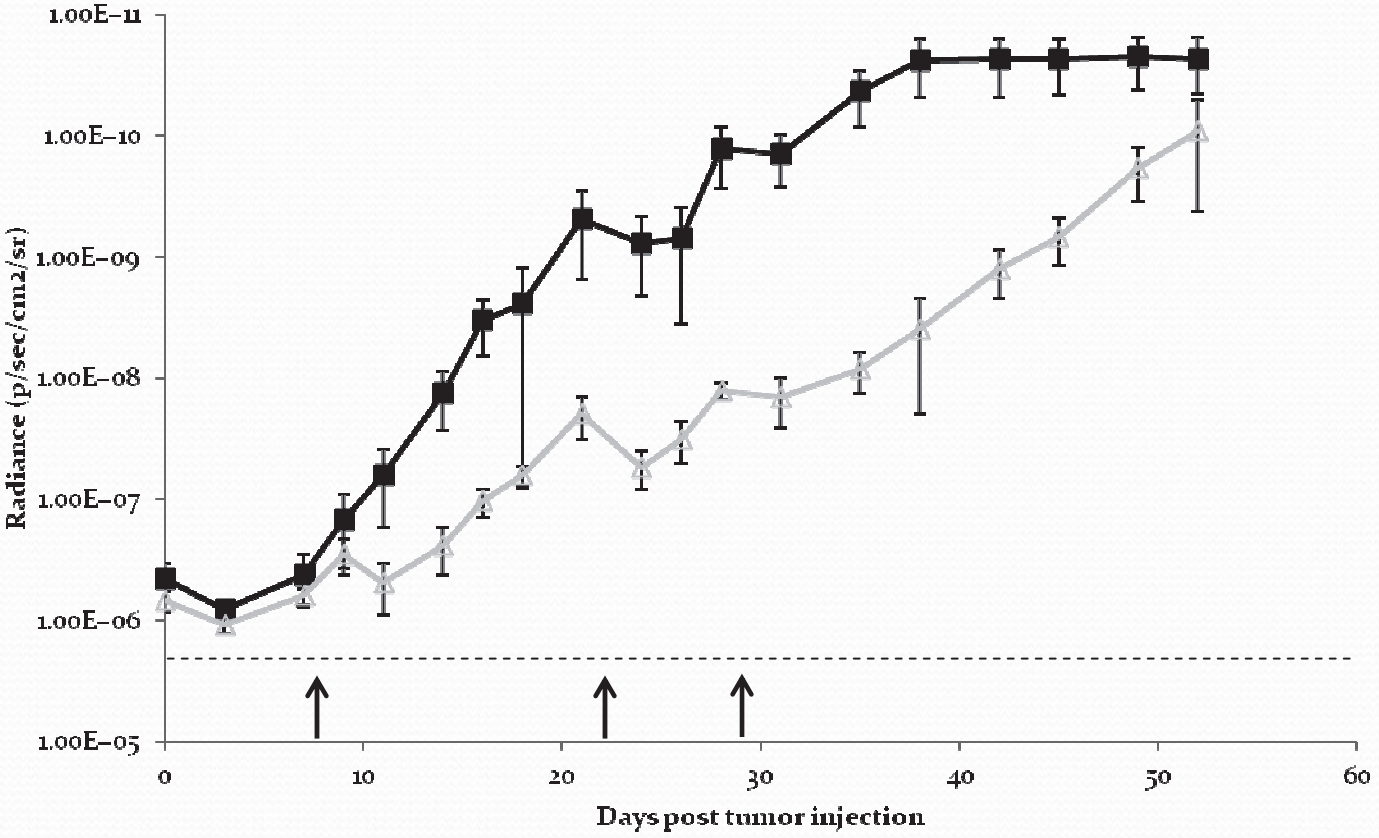
4X

5 days after first CAR T-cell administration I.T.

GD2 RNA CARs for disseminated NB



GD2 RNA CARs for disseminated NB



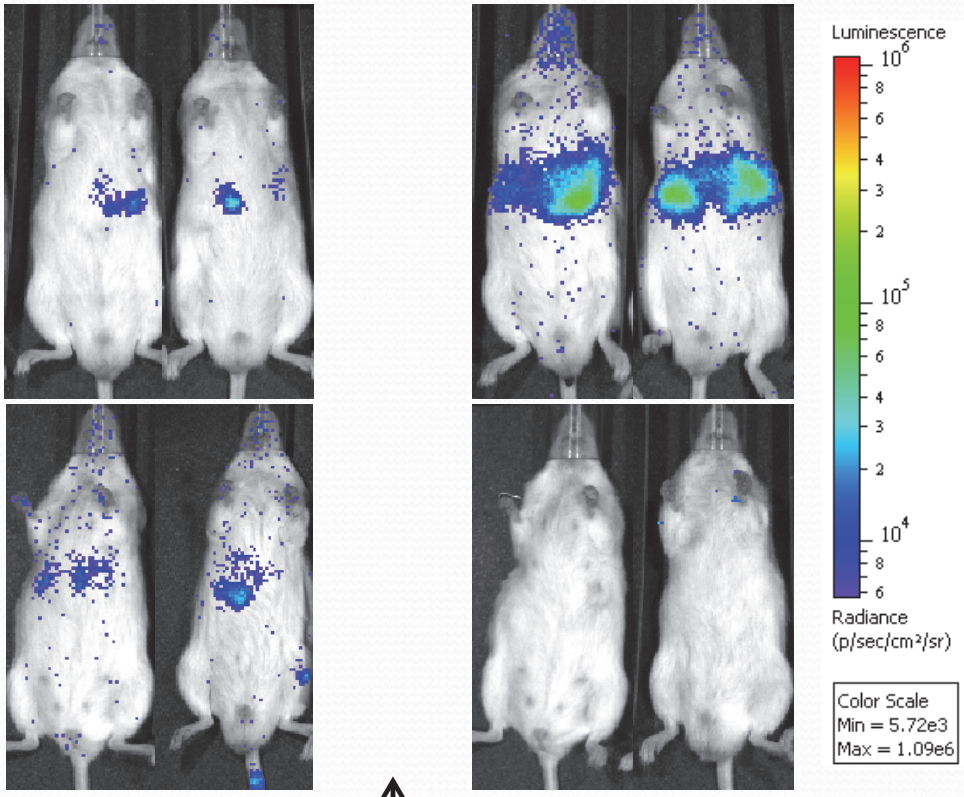
↑ RNA T-cells
Day 8: 5 x 10^6
Day 22: 1.5 x 10^7
Day 29: 1.5 x 10^7

GD2 Lenti CARs for disseminated NB

Day 13 Day 21

CART19

GD2 CAR

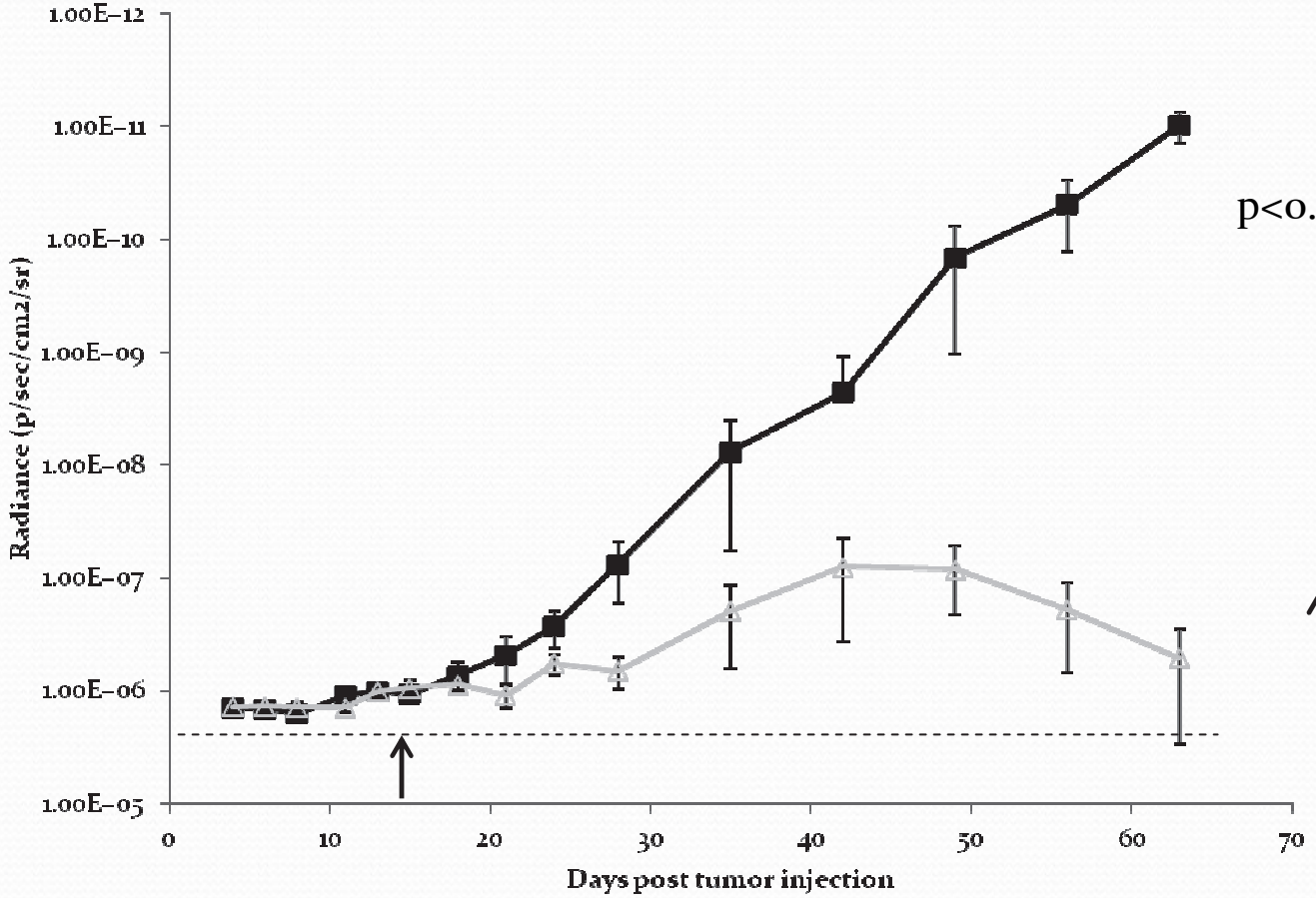


↑ T-cell administration

CD19: 1 x 10^7 (55% CAR+)

GD2: 1 x 10^7 (11% CAR+)

GD2 Lenti CARs for disseminated NB



p<0.001

↑T-cell administration

CD19: 1 x 10^7 (55% CAR+)

GD2: 1 x 10^7 (11% CAR+)

Conclusions

- Permanently-modified CAR T-cells can have significant impact on both liquid and solid tumors

- Transiently-modified CAR T-cells can mediate successful anti-tumor responses in liquid and solid tumors
  - Multiple doses
  - Lymphodepletion between doses
  - Dosing schedule

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